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Lasserson, Daniel S; Shine, Brian; O'Callaghan, Christopher A; James, Tim

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Requirement for cystatin C testing in chronic kidney disease: retrospective population-based study

Lasserson DS[1,2], Shine B[3], O'Callaghan CA[2], James T[2]

[1]Institute for Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT

[2] Nuffield Department of Medicine, University of Oxford, Oxford OX3 7BN.

[3] Department of Clinical Biochemistry, John Radcliffe Hospital, Oxford, OX3 9DU

Correspondence to Prof D Lasserson D.S.Lasserson@bham.ac.uk

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Abstract

Background: Creatinine based estimated glomerular filtration rate (eGFR) determines chronic kidney disease (CKD) stage, but under estimates renal function. The 2014 updated NICE guidance recommends that GPs reduce over diagnosis of CKD stage 3a (eGFR 45 – 60 ml/min/1.73m^2) by using the renal biomarker cystatin C.

Aim: To determine the population requirement for cystatin C testing compared with the current national availability of the assay.

Design and setting: Retrospective study of primary care laboratory requests in Oxfordshire

Method: We analysed first creatinine results from tests ordered in primary care over a six year period (2008 – 2014) in a population of 600,000 in Oxfordshire. We determined the number of patients with CKD stage 3a without proteinuria (requiring cystatin C to implement NICE guidance). A conservative estimate of the national need was provided by scaling the population of Oxfordshire to the national population (CKD prevalence is below the national average). We determined cystatin C assay availability using national databases of laboratory assay provision.

Results From a population of 600,000, there were 22,240 individuals with stable stage 3a CKD and no proteinuria. As the population of Oxfordshire represents 1% of the UK population, there is an initial requirement for at least 2 million people to have their CKD status determined with cystatin C testing. Eight laboratories reported cystatin C assay provision (2.1% of UK laboratories).

Conclusion: There is a substantial gap between cystatin C assay requirement in primary care and national assay provision. This is a major barrier to implementing NICE guidance.

How this fits in

- Cystatin C based eGFR improves accuracy of CKD staging and is recommended by NICE
- We have determined the large scale of cystatin C testing that will be needed for accurate diagnosis in primary care
- A tiny proportion of UK laboratories can test for cystatin C
- Unless commissioners address this assay provision gap, NICE guidance can't be implemented leaving patients at risk of over diagnosis, unnecessary prescribing and unnecessary laboratory monitoring

Introduction

Chronic kidney disease (CKD) increases mortality and healthcare resource usage[1] and the majority of patients with CKD are diagnosed and managed in general practice. CKD is staged according to estimated glomerular filtration rate (eGFR) and level of proteinuria.[2] eGFR is routinely calculated from serum creatinine, which is cheap to analyse and universally available, but at higher levels of measured GFR, the eGFR formulae have a tendency to under-estimate true renal function.[3] This results in over-diagnosis of CKD and in itself increases costs to healthcare and unnecessary burden for patients.

Cystatin C is an alternative biomarker of renal function, which displays less variation due to muscle mass than creatinine and offers greater accuracy of GFR estimation which improves the relationship between eGFR and subsequent risk of CKD-related outcomes - cardiovascular death and end-stage renal failure.[4]

In the UK, the National Institute for Health and Care Excellence (NICE) has published revised guidance for the diagnosis and monitoring of CKD.[5] Recognising that the newly recommended CKD-EPI equation for estimating eGFR from creatinine still has bias at higher levels of eGFR[3], NICE recommend testing with cystatin C for patients whose eGFR calculated from serum creatinine is in the stage 3a range (45 – 59 ml/min/1.73m^2). Whilst there are many formulae that can transform cystatin C into eGFR,[6-10] the NICE guidance recommends the CKD-EPIcys equation which combines creatinine and cystatin C.[5] Use of the CKDEPIcys equation to determine eGFR in large prospective cohort studies improves the classification of risk compared with the standard creatinine based CKD-EPI equation.[4]

Irrespective of the choice of equation to transform cystatin C, there is likely to be a substantial need for UK laboratories to offer cystatin C testing to general practice at substantial scale and pace if NICE

guidance is to be implemented within a reasonable time frame. We set out to determine the likely population need for cystatin C testing and to compare this with the current scale of provision using two indicators of laboratory availability of the assay.

Methods

We determined the proportion of patients in primary care in a population of 600,000 in Oxfordshire[11] who would require testing with cystatin C as part of CKD diagnosis and monitoring in accordance with NICE guidance. We analysed first creatinine results from tests ordered in primary care over a six year period (2008 – 2014) to assess the scale of the need for cystatin C testing and the stability of this requirement over time. The clinical biochemistry laboratory at the John Radcliffe Hospital used a modified Jaffe analytical technique with materials traceable to isotope dilution mass spectrometry methods, so creatinine assay results were standardised throughout the time period of analysis. We calculated eGFR from creatinine using the CKD-EPI equation and we determined the number of patients with stable stage 3a CKD - patients with a minimum of two eGFR results in the 3a range (45 – 60 ml/min/1.73m^2) at least three months apart. For patients with a first eGFR result in the 3a range in the last sampled year, 2014, we looked for follow up tests in the 12 months after the end of the sampling window in order to determine whether they had stable 3a CKD... We then excluded patients with an albumin:creatinine ratio greater than 3 mg/mmol as these patients are deemed to have CKD and do not need additional testing with cystatin C.[5] Therefore the 'catch up' testing required in the population to meet NICE guidance would be the remaining patients with stable stage 3a CKD without proteinuria.

Two indicators of cystatin C assay availability were obtained. UK laboratories are required to participate in proficiency testing to achieve accreditation. The United Kingdom External Quality Assessment Service (UKNEQAS) represents a network of proficiency testing schemes, one of which offers clinical laboratories a service to assess the performance of markers of GFR including creatinine and cystatin C. We ascertained from the scheme provider the number of laboratories participating in

the UKNEQAS quality assessment scheme for both cystatin C and creatinine at two time points one year apart to assess for growth in capacity. The second approach was to search for cystatin C on the website AssayFinder,[12] a widely used web resource that enables identification providers of specific laboratory testing.

Results

From 2008-2014, a total of 29,987 individuals had evidence of stable stage 3a CKD. Of these, 7,747 patients had an ACR > 3mg/mmol, leaving 22,240 patients without evidence of proteinuria. In addition, a further 3,875 patients had one eGFR in the stage 3a range but no further blood tests within the 6 year sampling frame.

Table 1 shows the numbers of patients with stable 3a CKD in each year and the number with an ACR > 3 mg/mmol. The number of new individuals requiring cystatin C testing falls each year as population coverage of prevalent cases increases with time from different blood testing practices in the community. As the population of Oxfordshire represents around 1% of the UK population, [11] and assuming that the level of primary care blood testing is similar in other areas of the UK, there is an initial requirement for at least 2 million people to have their CKD status determined with cystatin C testing.

As of April 2015, four laboratories reported cystatin C on the UKNEQAS scheme for GFR estimations compared to 340 reporting creatinine, representing 1.2 % of participating laboratories. In June 2016 the comparative enrolment was 8 reporting cystatin C and 378 reporting creatinine, 2.1 % of participants. In April 2015 the AssayFinder website documented three UK laboratories offering cystatin C analysis and this figure was unchanged by July 2016.

Discussion

Summary

A substantial number of patients will require additional testing with cystatin C if the latest NICE CKD guidance is to be implemented. Although we observed a reduction, over a 5 year period, in the proportion of all eGFR results from primary care that are in the CKD 3a range, there were still large numbers of patients whose CKD status cannot be fully determined with creatinine-based measures alone. Our findings from two independent estimates of routine cystatin C availability suggest that only a few laboratories have this assay available with an accredited testing process and there has been very little increase in availability over the past 12 months. This implies that there is a very large gap between need for the cystatin C assay, in order to implement NICE guidance, and its provision in routine UK healthcare.

Strengths and Limitations

Limitations of our assessment of cystatin C test availability using the enrolment in UKNEQAS include the possibility that UK laboratories are enrolled with different scheme providers. We are aware through our own laboratory participation of another proficiency testing organisation, the Swedish EQUALIS scheme, which provides a service across Europe. Five of the 51 participating laboratories were in the UK.. The limitation of using AssayFinder as an indicator is that not all UK laboratories use this website. However, despite the potential limitation of our approaches the two indicators are consistent in suggesting only very limited provision. Cystatin C can be undertaken on a wide range of commonly available instruments[6] suggesting this is not a factor in routine availability. Furthermore, whilst our estimate of the UK wide requirement for cystatin C testing rests on a number of assumptions, we believe that it is a conservative estimate, given that the prevalence of CKD in Oxfordshire is lower than the average for clinical commissioning group regions in England.[13]

Nevertheless our analysis has significant strengths. We took a population-based approach to include all patients who are currently tested and monitored in primary care over time, allowing us to determine the population to which the NICE guidance is applicable. Standardised creatinine assays were used by the laboratory during 2008 – 2014 so there will be very little variation over time in

laboratory methods and we used the CKD-EPI formula to calculate eGFR, in keeping with the most recent recommendation from NICE.

Comparison with existing literature

To our knowledge, there has been no other attempt to quantify the need for cystatin C testing in a contemporary patient population with renal function testing by general practitioners. Furthermore there has been very little published on the barriers to implementing current NICE guidance for CKD in primary care.

Implications for clinical practice

Cystatin C testing is only provided in a small minority of clinical chemistry laboratories at present and this represents a significant barrier to implementing the diagnostic algorithm of the new NICE guidance for primary care. Nationally, this means that there are large numbers of patients whose CKD status cannot be determined according to current NICE guidance on the diagnosis and management of CKD.

This raises a major issue for GPs because they will be unable to meet a national recommendation and therefore could be seen to fail their patients, according to this NICE criterion of optimal assessment of renal health. However, this is due to a lack of access to a diagnostic test, the availability of which was not mandated by NICE prior to the release of the guidance. This exemplifies a general problem which arises when guidelines are released without prior assessment of the practical requirements for their implementation. There are strategies that can minimise this problem, notably the Dutch College of General Practitioners has a well-established programme of producing evidence-based guidelines with education and professional development, alongside ensuring that there is adequate access to the investigations that are recommended.[14]

We suggest that Clinical Commissioning Groups should identify how best to commission diagnostic services to support GPs in implementing NICE guidance to ensure accurate diagnosis and monitoring of CKD in their registered populations.

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Ethical Review

Not required: Aggregate anonymised laboratory data accessed only by the clinical laboratory team as part of NICE guidance readiness assessment.

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Table 1 Number of individuals with stable CKD stage 3a by year of first test, sub group with proteinuria and cumulative total over a six year testing window.

Year	Individuals with evidence of stable CKD 3a	Individuals with ACR > 3 mg/mmol	Cumulative total with stable 3a CKD who would require cystatin C testing
2008	20129	5094	15035
2009	4195	1159	18071
2010	2208	624	19655
2011	1146	317	20484

2012	988	219	21253
2013	735	202	21786
2014	586	132	22240